

REMARKS

I. Status of the Claims

Claims 1-10 are pending in the application, and claims 4-10 stand withdrawn. Thus, claims 1-3 are under consideration and stand objected to and/or rejected under 35 U.S.C. §112, first paragraph. The specific grounds for objection/rejection are set forth in detail below.

II. Objections

A. Claims

Claims 1-3 are objected to for reciting non-elected subject matter. The claims have been amended to recite only the elected sequences.

B. Sequences

The disclosure is objected to for lack of a sequence identifier for the sequence provided in FIG. 1. A new sequence listing and amendment to the specification are provided.

III. Enablement

Claims 2 and 3 are rejected as lacking an enabling disclosure for preventative or therapeutic embodiments across the full scope of the claims. Though claims 2 and 3 are drawn to compositions and methods, respectively, the enablement issue is in essence the same – whether one can use the composition of claim 2 to inhibit any or all of the diseases of claim 3. According to the examiner, there is insufficient evidence in either the instant specification or the prior art to indicate that decoy oligonucleotides can be used *in vivo*, and indeed, it is argued that such methods are unpredictable. Thus, the examiner believes that the burden is shifted to

applicants to defend the enablement of the claimed invention. To the extent that the rejection is based on “prevention” of disease, an amendment to claim 3 has removed this language. Applicants traverse as to the remainder of the rejection.

First, the examiner (citing Jen *et al.*, 2000 and Opalinska *et al.*, 2002) argues that delivery of therapeutic oligonucleotides *in vivo* to appropriate target cells is problematic. These references refer to the cellular uptake of antisense or RNAi oligonucleotides. Indeed, such oligonucleotides are not readily taken up by cells, and specific means for introducing these molecules (transfection) must be used in order to facilitate their transfer into cells. However, the “decoy” oligonucleotides of the present invention are distinct from antisense and RNAi oligonucleotides. While the latter are single stranded oligo-ribonucleotides, the “decoy” ODNs are short double-stranded oligo-deoxyribonucleotides (see definition of “decoy oligonucleotide” on page 6, line 4, of the application). Thus, the reference cited by the examiner as support for the rejection are not appropriate given the subject matter of the present invention.

Indeed, this difference (single-stranded RNA vs. double-stranded DNA) is quite important when addressing the issue of intracellular uptake. As described in the attached declaration of Dr. Markus Hecker, the inventor has shown, using fluorescence- and radio-labeled (³⁵S) STAT-1 decoy ODNs, that such oligonucleotides are *readily* taken up by cells without the help of *any* transfection agents. Declaration at paras. 2-5; Exhibit A at pages 2-4, 6-7, 9-10, 12-13, 15-17. This is in contrast to what is required for antisense and RNAi oligonucleotide transfer. This functional advantage, unique to short double-stranded oligo-deoxyribonucleotides of the present invention, significantly simplifies the use of such compositions. As a particular example, medication of subjects in clinical studies for asthma uses a simple aqueous solution of the active pharmaceutical ingredient, *i.e.*, a decoy oligonucleotide called AVT-01 decoy ODN that binds

the STAT-1 transcription factor; no additional transfection agent is required. A pilot clinical study with this medication (*i.e.*, AVT-01 decoy ODN) has demonstrated efficacy in humans which is, of course, only possible following successful transfer of the decoy ODN into host cells. This is also evidenced by mouse *in vivo* experiments, where AVT-01 decoy ODN efficiently entered bronchial epithelium. See Hecker Declaration at para. 6; Exhibit A at pages 19-22. These data effectively counter the examiner's enablement concerns.

Second, it is argued that while eNOS is associated with certain diseases (*e.g.*, cardiovascular disease), there is insufficient link between that target and all the diseases set forth in claim 3. In response, applicants direct the examiner to the attached papers. The first paper by Cattaruzza *et al.* (Exhibit B) deals with coronary heart disease and employs decoys having SEQ ID NO: 1 and 3. A specific SNP (single nucleotide polymorphism) in the promoter of nos-3 gene leads to impaired sensitivity to laminar shear stress. Laminar shear stress is the most important stimulus controlling NOS-3 expression in endothelial cells. NOS-3 is critical for blood pressure control and retardation of arteriosclerosis. Thus, an impaired response to shear stress results in an impaired control of blood pressure etc. and predisposes for coronary heart disease. Treatment of the cells with the respective decoys restored laminar shear stress sensitivity, *i.e.*, the binding of an inhibitory factor to the promoter was blocked. Thus, in patients having this SNP the decoy can serve as medicament for coronary heart diseases by restoring the natural sensitivity to laminar shear stress.

The second paper by Melchers *et al.* (Exhibit C) is an analogous study focusing on the same SNP but in view of rheumatoid arthritis. Rheumatoid arthritis is an inflammatory disease, *i.e.*, pro-inflammatory stimuli exceed anti-inflammatory stimuli. Anti-inflammatory stimuli can be mediated by IL-10 via the transcription factor STAT-3 which induces NO synthase 3 (NOS-

3). NOS-3 in turn produces nitric oxide, an inhibitor of pro-inflammatory gene expression. Thus, impairment of NOS-3 production leads to a loss of inhibition of pro-inflammatory gene expression, *i.e.*, an upregulation of pro-inflammatory stimuli. In this study, the authors showed that in patients having the same SNP as above in Cattaruzza *et al.*, STAT-3 cannot bind to the nos-3 promotor and thus does not induce NO synthase because the binding site is blocked by an inhibitory factor. Treatment with decoy again restored sensitivity to STAT-3. Thus, the decoy can serve as a medicament in rheumatoid arthritis in patients having the respective SNP by restoring sensitivity to anti-inflammatory stimuli.

Applicants submit that while there is no *in vivo* demonstration of use of the elected invention, the evidence of record, on balance, indicates that one of skill in the art could transfer the claimed decoy oligonucleotides into cells *in vivo* and achieve the same effects seen in *in vitro* experiments. Moreover, there is a sufficient nexus between NOS-3 and the various diseases as now claimed to support enablement thereof. As such, the enablement requirement has been satisfied, and the rejection is thus improper. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. The examiner is invited to contact the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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